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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/930,915	08/15/2001	Ashley J. Birkett	LOR-102.2 (81175)	2278

24628 7590 08/04/2008

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EXAMINER	
PENG, BO	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
08/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/930,915	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12-33,35-38 and 42-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-33,35-38 and 42-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/21/07 & 8/15/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 28, 2008, has been entered.

2. Claims 1-9, 12-33, 35-38 and 42-78 are pending, and are under consideration in this Office action.

Specification

3. The use of trademarks has been noted in this application, e.g. Superose ^{R}, [0094][0238], Bac-to-Bac^{TM}[0234], Alhydrogel^{TM} [0282][0283], and Montanide^{TM} [0285], etc. for example, throughout the text. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections – 35 USC § 112-Scope of enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. (**Restated rejection,** see Office action dated 5/9/2005, p. 7) Claims 1-9, 12-33, 35-38 and 42-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a HBc chimer of SEQ ID NO: 246-251, does not reasonably provide enablement for a HBc chimer containing up to about 5% substituted amino acid residues in the HBc SEQ ID NO: 246-251. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

6. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. In the present case, the factors that are considered most relevant are the presence or absence of working examples, the direction or guidance presented, and the nature of the invention.

7. Claims 1-9, 12-33, 35-38 and 42-78 specify a chimer molecule having enhanced particle stability and with up to about 5 percent substituted amino acid residues in the HBc sequences SEQ ID No: 246-251. The scope of claims encompasses a large number of HBc chimers that contain 5% substitutions variously arranged along the sequence of

SEQ ID No: 246-251. As a result, the claims encompass a large number of alleged HBc chimers with no defined structure but having enhanced particle stability. Although Applicant has disclosed that one species HBcΔ is used to construct HBc chimers in the specification, Applicant has not disclosed sufficient species of alternative HBc variants that have 5 percent substituted amino acid residues in the HBc sequences SEQ ID No: 246-251, and have enhanced particle stability. More importantly, the specification has not shown that such alleged HBc chimers containing 5% substitutions can still form viral-like particles like HBc. Applicant fails to provide the necessary guidance that would lead one to such molecules.

8. The prior art teaches that even a single substitution can have an unpredictable effect on the assembly of HBc particles. Metzger teaches that a single amino acid change, Pro-138 to Gly, prevents the HBc protein self-assembling into particles (Metzger, J. Gen. Virology, 79:587-590, 1998). Thus, a single amino acid can create problems resulting from changes in conformation that can't be adequately predicted in advance.

9. Thus, based on the disclosure in the application, and on the knowledge in the art, those skill in the art would not be able to make alleged stabilized HBc chimers containing 5% substituted amino acid residues in the HBc SEQ ID NO: 246-251.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. (**Prior rejection-maintained**) The rejection of Claims 1-9, 15, 16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78 under 35 U.S.C. 103(a), as being unpatentable over Pumpens et al. (1995) in view of Zlotnick et al (1997), **is maintained** for the reasons of record and reasons set forth below.

In response to Applicant's argument 1:

12. Applicant argues that Ulrich, Newman, and Lachman are researches worked in this filed, and knew of and cited Zlotnick's work and disrecarded it for dealing with particle stability.

13. This argument is not relevant. Even though Ulrich, Newman, and Lachman did not combine teachings of both Pumpens and Zlotnick, the knowledge of Pumpens and Zlotnick are still suggestive to those of ordinary skill in the art. In the instant claims, specifically, all basic structural feature limitations are taught or suggested by Pumpens and Zlotnick. Applicant has not explicitly pointed out which specific structures of the alleged HBc chimer are different from the prior art, and how they result in the alleged stability of the HBc chimer. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

In response to Applicant's argument 2:

Applicant argues same argument as that presented before: The cited references are not combinable. Specifically, no construct of Zlotnick contained heterologous epitope as claimed. Pumpens teaches insertion of heterologous sequences to enhance stability, which is an entirely different approach to Zlotnick and incompatible with the latter. As such, it is submitted that the two teachings are not appropriately combined in the Action and the rejection should be withdrawn (Remarks, p. 22).

14. Again, this argument is not convincing. “There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art.” Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

15. The cited Pumpens and Zlotnick references are combinable because they are related to the art of HBc particles. Both Pumpens and Zlotnick provide knowledge to one of ordinary skill in the art how to construct stable HBc chimers particles that substantially free of viral nucleic acids. “When there is a design need or market pressure to solve a problem and there are a finite number of identified predictable potential solutions, a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense”. The Supreme Court decision in *KSR International Co. v. Teleflex Inc.* 82 USPQ2d 1385 (2007). As discussed in the previous Office action dated July 26, 2004 (see e.g. p11-14), it was well known that HBc chimeras with c-terminal deletions (HBcΔ) does not “pack” viral RNA into HBc Particle, but HBcΔ particles were less stable than their full-length counterparts. Zlotnick clearly demonstrates that the addition of a cysteine residue to the c-terminal of HBcΔ results in enhanced stability of HBcΔ particles. One of ordinary skill in the art would have been

motivated to combine the teachings of Pumpens and Zlotnick because "a person of ordinary skill has good reason to pursue the known potential options within his or her technical grasp". Therefore, Pumpens and Zlotnick references are combinable to one of ordinary skill in the art.

In response to Applicant's argument 3:

16. Applicant provided following arguments in Remarks p. 23 regarding the teaching of Zlotnick:

> The Action first discusses the alleged contribution of the Zlotnick manuscript. The premise that Zlotnick teaches the *C*-terminal cysteine can stabilize an HBc chimer molecule as recited in the claims here cannot be agreed with. This premise is inconsistent with the statements and data provided therein by Zlotnick.
>
> For example, Zlotnick explicitly states: "[p]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other constructs, with or without DTT. These capsids were *indistinguishable* (emphasis added) by negative staining electron microscopy and sedimentation on sucrose gradients." (See page 9558, column I, paragraph 1, Results and Discussion section.) As a second example, Zlotnick reports: "[a]t a resolution of ~20A, the outer surface of the Aull- labeled [monomaleimidyl-undecagold-labeled] Cp*150 capsid is indistinguishable (emphasis added) from those of unlabeled Cp147 and Cp183 capsids, (cf. Fig. 4 Top)." (See page 9558, column 2, and paragraph 1) These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are not important for HBcA capsid formation or stability.

17. Applicant's citations of Zlotnick are not complete, and the conclusion is misleading. The following is the complete citation of Zlotnick from page 9558, column 1, paragraphs 1 and 2, Results and Discussion section):

> [P]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other Cp constructs (10, 15), with or without DTT. These capsids were indistinguishable by negative staining electron microscopy and sedimentation on sucrose gradients (data not shown). When reduced CP*150 capsids were stored without DTT for 2 days, >90% of the protein oxidized to form disulfide-bonded dimers (Fig. 2 *a*). These bonds stabilize the quaternary structure of the capsid, as attested by the observation that oxidized Cp*150 capsids—unlike CP*149 capsids or reduced Cp*150 capsids—are resistant to dissociation by 3.5 M urea (Fig. 2 *b*). Knowledge of the location of residue 150 (see below) indicates that this disulfide bond links two dimers (Fig. 1 *b*) and is distinct from the intradimeric disulfide observed in Cp proteins with native cysteines (16, 25).
>
> Generally, when Cp proteins are stored in a low ionic strength, high pH buffer

they do not polymerize (10). However, when stored in this buffer without DTT, Cp*150 dimers assemble into capsids, as determined by negative stain electron microscopy and analytical ultracentrifugation. A high proportion of the protein in these capsids is disulfide-bonded (Fig. 2 *a*). These data show that disulfide bond formation by Cp*150 can promote capsid assembly. Without disulfide formation, higher-order structures do not accumulate in storage buffer, i.e., the rate for dissociation is greater than the rate of association. Formation of these disulfide bonds stabilizes complexes against dissociation. Thus, under these conditions, Cp polymerization appears to involve an equilibrium between subunits, assembly intermediates, and capsids (36). We also note that, in capsids, the cysteine 150 residues from adjacent subunits must be close enough to one another to form a covalent bond, a distance of 4.6–7.4 Å between α carbons (37). (Underline emphasis added by the examiner)

18. In view of teachings recited above, one skilled in the art would conclude that Zlotnick explicitly teaches that Cp*150, which contains a *C*-terminus cysteine, is more stable than Cp*149, which does not contain a *C*-terminus cysteine. These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are important for HBcA capsid formation and stability.

In response to Applicant's argument 4:

Applicant asserts from Figure 2a of Zlotnick that the polyacrylamide gel shown therein depicts disulfide bonded *dimers* **not HBcA core protein capsid particles**. Those capsids are the entities recited in the claims to have enhanced stability. Applicant argues that nothing in Zlotnick has shown the capsids behave like dimers, See Remarks p.24. Applicant asserts "The present claims recite the stability of the particles assembled from those monomers and dimers. As such, a disclosure concerning the stability or lack thereof of dimers or monomers neither teaches nor suggests anything of relevance to the claimed subject matter whether taken alone or with any other disclosure" (Remarks, p. 24).

19. This argument is not convincing because while targeting Zlotnick Fig. 2 alone, Applicant again ignores the teachings in Zlotnick specifically related to **HBcA core protein capsid particles.** Specifically, Zlotnick shows capsid protein in Figure 2(b). Zlotnick teaches in Fig. 2(b) as recite: "(b) size exclusion chromatography of **capsid**

protein (particles) after exposure to 3.5 M urea. Samples are oxidized Cp*150 (solid line), Cp*150 with 130 mMDTT (dashed line) and Cp*149 (dotted line)". See Description of Fig. 2, right col. p. 9557. Here, oxidized Cp*150 is polymerized capsid, Cp*150 with 130 mM DTT is reduced Cp*150, containing both polymerized and disassociated capsid particles. Thus, Figure 2b simply shows that Cp*150, shown as single peak of capsid polymer, is more stable than Cp*149, shown as two peaks of polymerized and disassociated capsid.

20. Moreover, in Figure 3, Zlotnick teaches cryo-election microscopy of Cp149, Cp*150 capsid. In Figure 4, Zolonick shows image reconstruction of T = 4 HBV capsids. In Fig. 1b, Zlotnick teaches Cp150 dimers connected by a disulfide bond between Cys-150 residues (See e.g. 1b, Description of Fig. 1b, and page 9558, col. 1, paragraphs 1 and 2, Results and Discussion section). These figures clearly show that Cp*150 forms capsid particles assembled from HBc dimers!

In response to Applicant's argument 5:

21. Applicant further asserts that Cp150, which is HBc containing C-terminus Cys, failed to associate into dimer or has readily disassociated as shown in Zlotnick's Fig. 2a lane 6 and lane 7, suggesting Cp150 is not stable. (Remarks p. 26).

22. This argument is not relevant to the claims. Applicant argues the limitations that are not in the claims. The instant claims are directed to a genus of immunogenic particles that are comprised of a plurality of recombinant chimeric HBc protein molecules have a length of up to about 515 amino acids...". The instant claims do not require being absence of HBc monomer. Zlotnick shows in Fig. 2a that the vast majority of Cp150, which

contains no C-terminus Cys, is polymers (See lanes 6 and 7), while Cp149, which contains no C-terminus Cys, is monomers (See lane 5). Thus, Zlotnick shows that Cp150 is a polymerized HBc molecule, which meets the claim limitation.

23. Furthermore, Fig. 2b shows that Cp*150, shown as single peak of HBc polymer capsid, is more stable than Cp*149, shown as two peaks of polymerized and disassociated capsid. Thus, Zlotnick has demonstrated that C-terminus-Cys enhances stability of HBc.

24. The rejection is maintained for the reasons discussed above and set forth in the previous Office actions.

25. (**Prior rejection-maintained**) The rejection of Claims 12-14, 17, 27-29, 36, 37, 59-62 and 76 under 35 U.S.C. 103(a), as being unpatentable over Pumpens et al. (1995), in view of Zlotnick et al (1997) as applied to Claims 1-9, 15, 16, 18-26, 30-33, 35, 38, 42-58, 63-75, 77 and 78, further in view of Thornton et al. (US 5,143,726) **is maintained** for the same reasons of record.

In response to Applicant's argument:

Applicant argues that Thornton teaches use of modified amino acid side chains in HBc, but fails to identify where the modifications should go and fails to provide the specificity required if such a disclosure were to have been made in the present application. As such, the Thornton disclosure is not enabling for the use put to it by the Action because it not only does not put this claimed invention into the hands of the public, it does nothing to assist the public in grasping this invention. (Remarks, p. 29)

26. This argument is not convincing. Thornton specifically teaches that a polypeptide immunogen operatively link by a peptide bond to N-terminal flanking sequence, or C-terminal flanking sequence of HBc, or HBV core protein from about position 70 to about position 140 from the amino terminus thereof, See e. g. claims. These modification sites

in HBc taught by Thornton are consistent with the structural elements of the present application. Therefore, Thornton disclosure is enabling for the use put to it by the Action.

27. Since Applicant has not present any compelling reasons to overcome the 103 rejection, the rejection is maintained.

Remarks

28. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner
July 31, 2008